

Fig. 1

ATGTCCATGA	ACTGCTGAGT	GGATAAACAG	CACGGGATAT	CTCTGTCTAA	- 96
AGGAATATTA	CTACACCAGG	AAAAGGACAC	ATTCGACAAC	AGGAAAGGAG	- 46
CCTGTCACAG	AAAACCACAG	TGTCCTGTGC	ATGTGACATT	TCGCC	- 1
ATG GGA AAC AAC TGT TAC AAC GTG GTG GTC ATT GTG CTG CTG CTA	45				
Mbt Gly Asn Asn Cys Tyr Asn Val Val Val Ile Val Leu Leu Leu					
GTG GGC TGT GAG AAG GTG GGA GCC GTG CAG AAC TCC TGT GAT AAC	90				
Val Gly Cys Glu Lys Val Gly Ala Val Gln Asn Ser Cys Asp Asn					
TGT CAG CCT GGT ACT TTC TGC AGA AAA TAC AAT CCA GTC TGC AAG	135				
Cys Gln Pro Gly Thr Phe Cys Arg Lys Tyr Asn Pro Val Cys Lys					
• H4-1BB FI					
AGC TGC CCT CCA AGT ACC TTC TCC AGC ATA GGT GGA CAG CCG AAC	180				
Ser Cys Pro Pro Ser Thr Phe Ser Ser Ile Gly Gly Gln Pro Asn					
• H4-1BB FII					
TGT AAC ATC TGC AGA GTG TGT GCA GGC TAT TTC AGG TTC AAG AAG	225				
Cys Asn Ile Cys Arg Val Cys Ala Gly Tyr Phe Arg Phe Lys Lys					
• H4-1BB FIII					
TTT TGC TCC TCT ACC CAC AAC GCG GAG TGT GAG TGC ATT GAA GGA	270				
Phe Cys Ser Ser Thr His Asn Ala Glu Cys Glu Cys Ile Glu Gly					
TTC CAT TGC TTG GGG CCA CAG TGC ACC AGA TGT GAA AAG GAC TGC	315				
Phe His Cys Leu Gly Pro Gln Cys Thr Arg Cys Glu Lys Asp Cys					
AGG CCT GGC CAG GAG CTA ACG AAG CAG GGT TGC AAA ACC TGT AGC	360				
Arg Pro Gly Gln Glu Leu Thr Lys Gln Gly Cys Lys Thr Cys Ser					
• H4-1BB RI					
TTG GGA ACA TTT AAT GAC CAG AAC GGT ACT GGC GTC TGT CGA CCC	405				
Leu Gly Thr Phe Asn Asp Gln Asn Gly Thr Gly Val Cys Arg Pro					
• H4-1BB RII					
TGG ACG AAC TGC TCT CTA GAC GGA AGG TCT GTG CTT AAG ACC GGG	450				
Trp Thr Asn Cys Ser Leu Asp Gly Arg Ser Val Leu Lys Thr Gly					
ACC ACG GAG AAG GAC GTG GTG TGT GGA CCC CCT GTG GTG AGC TTC	495				
Thr Thr Glu Lys Asp Val Val Cys Gly Pro Pro Val Val Ser Phe					
TCT CCC AGT ACC ACC ATT TCT GTG ACT CCA GAG GGA GGA CCA GGA	540				
Ser Pro Ser Thr Thr Ile Ser Val Thr Pro Glu Gly Gly Pro Gly					
GGG CAC TCC TTG CAG GTC CTT ACC TTG TTC CTG GCG CTG ACA TCG	585				
Gly His Ser Leu Gln Val Leu Thr Leu Phe Leu Ala Leu Thr Ser					
GCT TTG CTG CTG GCC CTG ATC TTC ATT ACT CTC CTG TTC TCT GTG	630				
Ala Leu Leu Leu Ala Leu Ile Phe Ile Thr Leu Leu Phe Ser Val					
CTC AAA TGG ATC AGG AAA AAA TTC CCC CAC ATA TTC AAG CAA CCA	675				
Leu Lys Trp Ile Arg Lys Lys Phe Pro His Ile Phe Lys Gln Pro					
TTT AAG AAG ACC ACT GGA GCA GCT CAA GAG GAA GAT GCT TGT AGC	720				
Phe Lys Lys Thr Thr Gly Ala Ala Gln Glu Glu Asp Ala Cys Ser					

## Fig.1 cont'd

TGC CGA TGT CCA CAG GAA GAA GAA GGA GGA GGA GGA GGC TAT GAG 785  
 Cys Arg Cys Pro Gln Glu Glu Glu Gly Gly Gly Gly Gly Tyr Glu

CTG TGA  
 Leu ---

771

TGTA	CTATCC	TAGG	AGATGT	GTGG	GCCGAA	ACCG	GAGAAGC	ACTAG	GACCC	821
CACCA	TCCTG	TGGA	ACAGCA	CAAG	CAACCC	CACC	ACCCTG	TTCTT	ACACA	871
TCATC	CTAGA	TGAT	GTGTGG	GCGC	GCACCT	CATCC	AAGTC	TCTTC	TAACG	921
CTAAC	ATATT	TGTC	TTTACC	TTTT	TTTAAAT	CTTTT	TTTAA	ATTTA	AAATTT	971
TATGT	GTGTG	AGTG	TTTTGC	CTGC	CTGTAT	GCAC	ACGTGT	GTGTG	GTGTG	1021
GTGTG	TGACA	CTCT	GATGC	CTGA	GAGGTT	CAGA	AAGACAA	AGGGT	TGGTT	1071
CCATA	AAGAAC	TGGAG	TTATG	GATGG	CTGTG	AGCCG	GNNNG	ATAGG	TCGGG	1121
ACGGAG	ACCT	GTCTT	CTTAT	TTTAA	ACGTGA	CTGTAT	<u>ATA</u>	<u>AAA</u>	AAAAAAT	1171
GATATT	TCGG	GAATT	GTAGA	GATTG	TCCTG	ACACC	CTTCT	AGTTA	ATGAT	1221
CTAAG	AGGAA	TTGTT	GATAC	GTAGT	ATACT	GTATAT	GTGT	ATGTAT	ATGT	1271
ATATG	TATAT	ATAAG	ACTCT	TTTACT	GTCA	AAGTCA	AACCT	AGAGT	GTCTG	1321
GTTACC	AGGT	CAATTT	TATT	GGACAT	TTTTA	CGTCA	CACAC	ACACAC	CACAC	1371
ACACAC	CACAC	ACGTT	TATAC	TACGT	ACTGT	TATCG	GTTAT	CTACG	TCATA	1421
TAATG	GGATA	GGGTA	AAAAGG	AAACCA	AAAGA	GTGAG	TGATA	TTATT	GTGGA	1471
GGTGAC	CAGAC	TACCC	CTTCT	GGGTAC	GTAG	GGACAG	ACCT	CCTTC	GGACT	1521
GTCTAAA	ACT	CCCCT	TAGAA	GTCTC	GTCAA	GTTCC	CGGAC	GAAGAG	GACA	1571
GAGGAG	CAC	AGTCC	GAAAA	GTTAT	TTTTTC	CGGCA	AAATCC	TTTCC	CTGTT	1621
TCGTGAC	ACT	CCACCC	CTTG	TGGAC	ACTTG	AGTGT	CATCC	TTGCG	CCGGA	1671
AGGTCAG	GTG	GTACCC	GTCT	GTAGG	GCGG	GGAGAC	AGAG	CCGCG	GGGGA	1721
GCTACG	AGAA	TCGACT	CACA	GGGCG	CCCCCG	GGCTT	CGCAA	ATGAA	ACTTT	1771
TTTAAT	CTCA	CAAGT	TTTCGT	CCGGG	CTCGG	CGGAC	CTATG	GCGTC	GATCC	1821
TTATTAC	CCTT	ATCCT	GCGCG	CAAGAT	AAAA	CAACCA	AAAAG	CCTTG	ACTCC	1871
GGTACTA	AATT	CTCCCT	GCCG	GCCCC	CGTAA	GCATA	AACGCG	GCGAT	CTCCA	1921
CTTTAAG	AAC	CTGGC	CGCGT	TCTGC	CTGGT	CTCGC	TTTCG	TAAAC	GTTTC	1971
TTACAAA	AGT	AATTAG	TCT	TGCTTT	CAGC	CTCCA	AGCTT	CTGCT	AGTCT	2021
ATGGCAG	CAT	CAAGG	CTGGT	ATTTG	CTACG	GCTGAC	CGCT	ACGCC	GCCGC	2071
AATAAGG	GTA	CTGGG	CGGCC	CGTCG	AAGGC	CCTTT	GTTTT	CAGAA	ACCCA	2121
AGGCCCCC	CT	CATACCA	ACG	TTTCG	ACTTT	GATTCT	TGCC	GGTAC	GTTGGT	2171
GGTGGGT	GCC	TTAGCT	CTTT	CTCGAT	AGTT	AGAC				2205

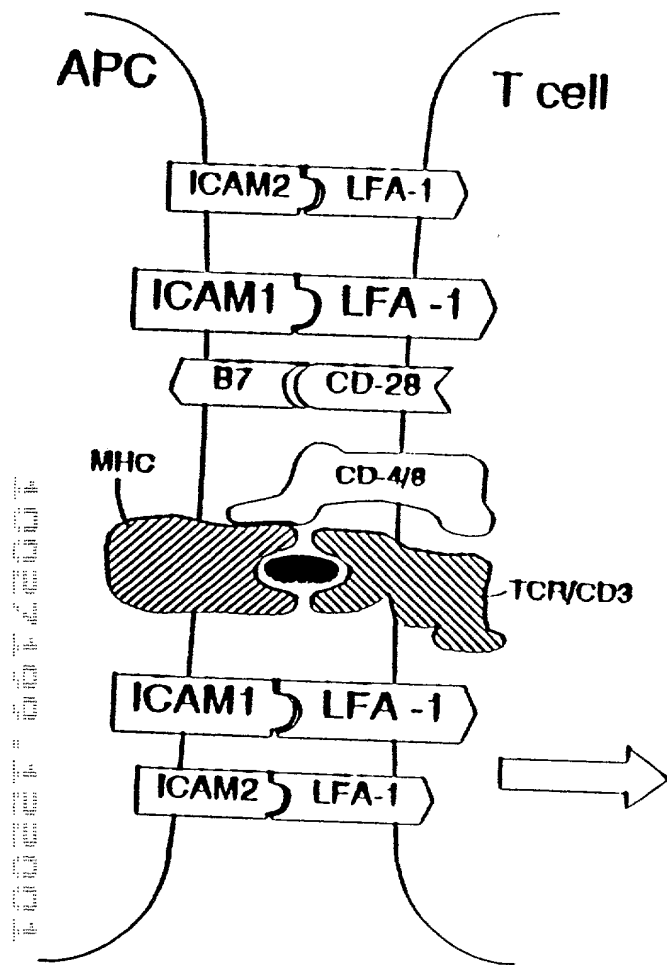
*Fig. 2a*

human homologue of mouse 4-1bb  
h4-1bb Length 838

1	AATCAGCTTT	GCTAGTATCA	TACCTGTGCC	AGATTTTCATC	ATGGGAAACA
51	GCTGTTACAA	CATAGTAGCC	ACTCTGTTGC	TGGTCCTCAA	CTTTGAGAGG
101	ACAAGATCAT	TGCAGGATCC	TTGTAGTAAC	TGCCCAGCTG	GTACATTCTG
151	TGATAATAAC	AGGAATCAGA	TTTGCAGTCC	CTGTCCTCCA	AATAGTTTCT
201	CCAGCGCAGG	TGGACAAAGG	ACCTGTGACA	TATGCAGGCA	GTGTAAAGGT
251	GTTTTTCAGGA	CCAGGAAGGA	GTGTTTCCTCC	ACCAGCAATG	CAGAGTGTGA
301	CTGCACTCCA	GGGTTTCACT	GCCTGGGGGC	AGGATGCAGC	ATGTGTGAAC
351	AGGATTGTAA	ACAAGGTCAA	GAAC TGACAA	AAAAAGGTTG	TAAAGACTGT
401	TGCTTTGGGA	CATTTAACGA	TCAGAAACGT	GGCATCTGTC	GACCCTGGAC
451	AAACTGTTCT	TTGGATGGAA	AGTCTGTGCT	TGTGAATGGG	ACGAAGGAGA
501	GGGACGTGGT	CTGTGGACCA	TCTCCAGCTG	ACCTCTCTCC	GGGAGCATCC
551	TCTGTGACCC	CGCCTGCCCC	TGCGAGAGAG	CCAGGACACT	CTCCGCAGAT
601	CATCTCCTTC	TTTCTTGCGC	TGACGTGCGAC	TGCGTTGCTC	TTCTTGCTGT
651	TCTTCCTCAC	GCTCCGTTTC	TCTGTTGTTA	AACGGGGCAG	AAAGAAACTC
701	CTGTATATAT	TCAAACAACC	ATTTATGAGA	CCAGTACAAA	CTACTCAAGA
751	GGAAAGATGGC	TGTAGCTGCC	GATTTCCAGA	AGAAGAAGAA	GGAGGATGTG
801	AACTGTGAAA	TGGAAGTCAA	TAGGGCTGTT	GGGACTTT	

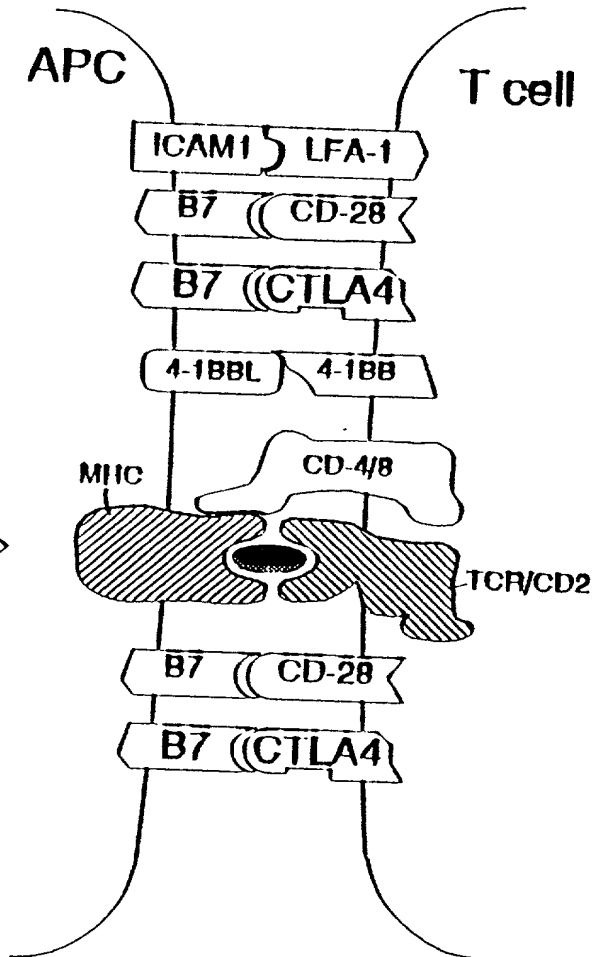
*Fig. 2b*

1	MGNSCYNIVA	TLLLVLNFER	TRSLQDFCSN	CPAGTFCDNN	RNQICSPCPP
51	NSFSSAGGQR	TCDICRQCKG	VERTRKECSS	TSNAECDCTP	GFHCLGAGCS
101	MCEQDCKQGQ	ELTKKGCKDC	CFGTFNDQKR	GICRPWTNCS	LDGKSVLVNG
151	TKERDVVCGP	SPADLSPGAS	SVTPPAPARE	FGHSPQIISF	FLALTSTALL
201	FLLFFLTLRF	SVVKRGRKKL	LYIFKQPFMR	PVQTTQEEDG	CSCRFPEEEE
251	GGCEL				



COGNITIVE PHASE  
early activation

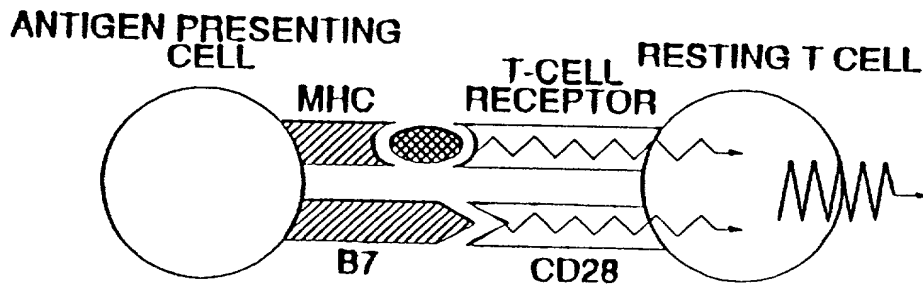
*Fig. 3a*



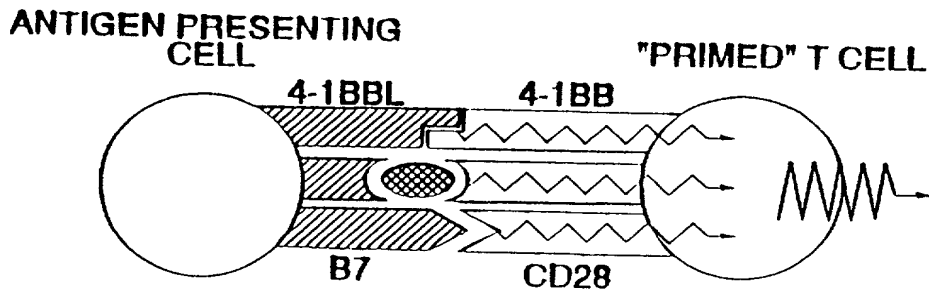
PROLIFERATION  
CLONAL EXPANSION  
late activation

*Fig. 3b*

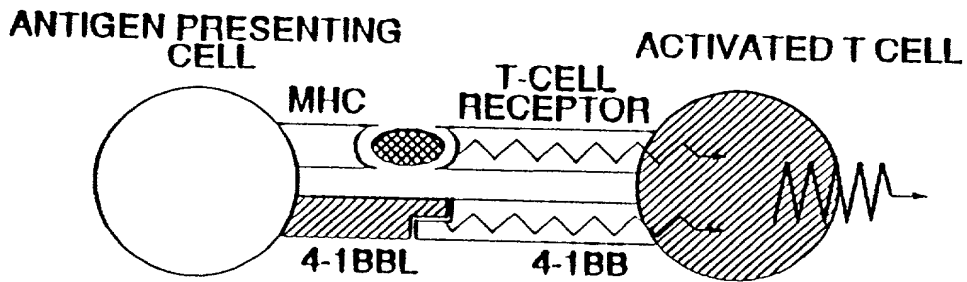
# NORMAL T-CELL ACTIVATION PATHWAY



*Fig. 4a*



*Fig. 4b*



*Fig. 4c*

## BLOCKING STEPS IN T-CELL ACTIVATION PATHWAY

